REMARKS

Applicants gratefully acknowledge withdrawal of the 35 USC § 101 rejection against claims 1, 2, 5, 6, 9, 13-24, 27-28, 30-39, and 42-55 made in the Office Action mailed August 10, 2005.

Claim Amendments

Claim 52 is currently amended. The amendments are made solely to clarify the dependency of the claim. Thus, the amendments do not introduce new matter.

The 35 USC § 101 Rejection

Claims 25 and 26 remain rejected under 35 USC § 101 on the basis that the claimed invention allegedly lacks patentable utility. Specifically, the Office alleges that any mouse or cortical cell culture could be used to make the claimed measurement. The Office further argues that a BACE-1 knockout mouse or a cortical cell culture derived therefrom is not required for the measurement to be made. Applicants respectfully traverse the rejection.

Claims 25 and 26 are directed to methods of analyzing potential side-effects for an inhibitor of beta-secretase comprising exposing a transgenic mouse comprising at least one nonfunctional allele of beta-secretase-1 (BACE-1) gene or a cortical cell culture derived therefrom, and measuring the changes in at least one component of the transgenic mouse or cortical cell responsive to the inhibitor.

Among other utilities discussed in the specification and in the previous responses dated October 28, 2004, June 27, 2005, and February 10, 2006, the claimed transgenic mice and cells have a well-defined use for determining the toxicity and/or side effects of BACE-1 inhibitors, which is particularly useful in the development of therapeutics for the treatment and/or prevention of Alzheimer's disease. For example, transgenic mice that are homozygous for a defective BACE-1 allele, or cortical cell culture derived therefrom can be used to assess whether the toxicity of an inhibitor is dependent on the inhibition of BACE-1 or on another biological mechanism. In other words, one can administer an inhibitor to the homozygous knockout mouse or cortical cell culture to see if it has any toxic effects other

than what might result from the inhibition of BACE-1 (see paragraph [62]). It is not possible to observe such effect in "any animal" or "any cortical cell culture," including an animal or cortical cell culture having wild-type BACE-1, as the Office asserts. Only the homozygous BACE-1 knock-out mouse would allow one to assess the toxicity effect of an inhibitor that is independent from the effect of BACE-1 inhibition.

Likewise, transgenic mice that are heterozygous for a defective BACE-1 allele, or cortical cell culture derived therefrom are useful to assess the toxicity and dosage concerns of a BACE inhibitor. The heterozygous BACE-1 knockout mouse or cortical cell culture provides a model for testing the effect of inhibitors when less BACE-1 enzyme is present as a way of assessing dosage. For example, a particular dosage of inhibitor may not have an observable toxic effect in animals or cortical cell culture having a wild-type level of BACE-1, but the same dosage could show toxicity or an altered biological effect in animal having less BACE-1 enzyme or no BACE-1 enzyme. In having altered levels of BACE-1 enzyme, both the heterozygous and homozygous BACE-1 knockout mice are particularly useful for assessing the toxicity of a BACE inhibitor as well as assessing the dosage effects of an inhibitor.

As explained above, transgenic homozygous and heterozygous BACE-1 knockout mice or cortical cell culture derived therefrom have altered levels of BACE-1 enzyme, and are thus useful for a toxicity analysis in a manner that is different from a toxicity analysis performed in animals or cortical cell culture having a wild-type BACE-1 gene. Thus, the Applicants submit that claims 25 and 26 do have patentable utility. Accordingly, the Applicants respectfully request withdrawal of the 35 U.S.C. §101 rejection.

The 35 USC § 112, First Paragraph, Rejections

Claims 1-2, 5-6, 9, 13-28, 30-39, and 42-55 are rejected under 35 USC § 112, first paragraph, as allegedly failing to teach one skilled in the art how to make and use the claimed invention. Specifically, the Office alleges that the methods of assay for an inhibitor of the production by a protease other than BACE-1 of an amyloid peptide recognized by an antibody that recognizes residues 13-28 of Aβ requires the mouse to be homozygous for BACE-1 disruption. Applicants respectfully traverse the rejection.

The standard for enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. M.P.E.P. §2164.08. The Applicants submit that one of skill in the art could make and use the claimed nonhuman animals, without undue experimentation. "The test of enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214, 217-19 (CCPA 1976)); M.P.E.P. §2164.06. Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.,* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Furthermore, the fact that the experimentation needed is complex is not determinative on the issue of whether the experimentation is undue, so long as the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983).

For all of the reasons presented in previous responses and for all of the reasons discussed above, the specification clearly teaches one skilled in the art how to use the claimed invention. For example, the specification teaches that the presently claimed transgenic homozygous and heterozygous BACE-1 knockout mice and corresponding cells can be used to analyze potential side-effects (e.g., determine the toxicity profile) of an inhibitor of beta-secretase by exposing the transgenic mouse to an inhibitor of beta secretase and measuring a change in the level of at least one component of the transgenic mouse wherein such change indicates a potential side effect. The specification also teaches the use of claimed transgenic homozygous and heterozygous BACE-1 knockout mice or corresponding cells for screening for agents that inhibit protease other than beta-secretase that are implicated in the production of Aβ or fragments thereof. See paragraph [61]. A significant decrease in beta-secretase levels was observed in heterozygote mice. See paragraph [79]. It was known in the art at the time of invention that other protease activities are also associated with Aβ production and therefore associated with Alzheimer's disease. Thus, one of skill in the art would have been enabled from the disclosures in the

specification coupled with information known in the art to use claimed heterozygote mice to screen for inhibitors of proteases other than BACE-1 without undue experimentation.

The Office further alleges that claims 21, 22, 52-55 are not enabled because the specification allegedly does not enable another peptide recognized by antibodies to residues 13-28 of Aβ other than Aβ. Applicants respectfully traverse the rejection.

The specification does enable another peptide recognized by antibodies to residues 13-28 of Aβ. The specification teaches that Aβ is a peptide of 39-43 amino acids and has several natural occurring forms. Further, the specification teaches the APP precursor. See, for example, paragraphs [36], [38], [39], and [40]. Thus, the specification enables the claimed invention, and it would not have been undue burden to one of skill in the art to make and use of the claimed invention.

With respect to claims 13-16, and 46-49, the Office alleges that the specification only enables the production of the double-transgenic mouse where a promoter regulates expression of the FAD-APP DNA sequence. The Office further asserts that the DNA sequence of FAD-APP must be integrated into the genome. Applicants respectfully traverse the rejection.

The claim is to be read in view of the specification. See *Phillips v. AWH Corp.*, 75 USPQ2d 1321 (Fed. Cir. 2005). The specification teaches in details the production of a single transgenic animal. The specification also teaches the production of a double-transgenic animal by breeding a transgenic animal with a functional inactivation of BACE-1 with a transgenic animal expressing a mutated form of human APP. See, for example, paragraphs [57], [58], and [59]. Claims 13-16, and 46-49 are enabled by the specification which teaches the production of a double-transgenic mouse where a promoter regulates the expression of the transgene incorporated into the genome. Thus, claims 13-16, and 46-49 are enabled by the specification. Hence, the rejection under 35 U.S.C. §112 first paragraph for allegedly lacking enablement against claims 13-16, and 46-49 is improper.

Additionally, the Office alleges that claims 25 and 26 are not enabled as to what parameter is being measured. Applicants respectfully traverse the rejection.

The specification teaches the use of the claimed transgenic mouse or corresponding cells to determine any side effects of compounds that are known to be inhibitors of beta-secretase. The side effects, or toxicity profile, can be determined by monitoring expression of a large number of mRNAs or proteins encoded thereby. The specification teaches the use of arrays for expression monitoring. Such arrays are readily available from sources such as Affymetrix. See paragraph [62]. Arrays are well known technique in the art and have been widely used in molecular biology research. Thus, one reasonably skilled in the art could make and use the invention from the disclosures in the specification coupled with information known in the art without undue experimentation. Accordingly, Applicants submit that claims 25 and 26 are enabled by the specification.

Based on the foregoing, the Applicants respectfully request reconsideration and withdrawal of rejections under 35 U.S.C.§112, first paragraph against claims 1-2, 5-6, 9, 13-28, 30-39, and 42-55 for allegedly failing the enablement requirement.

The 35 USC § 112, Second Paragraph, Rejections

Claims 34, 35, and 52 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office alleges that the recitation "a blastocyst formed by differentiation of a mouse embryonic stem cell" in claim 34 is indefinite. The Applicants traverse the rejection.

It is well understood by one of skill in the art the use of blastocysts to generate transgenic animals. It is the standard practice, and is further described in the specification, that the modified embryonic stem cells are combined with blastocysts to generate transgenic animals. The ES cells colonize the embryo and in some embryos form or contribute to the germline and eventually differentiate and develop into the resulting chimeric animal. See paragraphs [30], [57], and [84]. Thus, the Applicants submit that the claimed "blastocyst formed by differentiation of a mouse embryonic stem cell" is not indefinite because it is well understood by one of skill in the art.

Additionally, the Office alleges that claim 35 is indefinite for reciting "breeding the chimeric mice with the mice of the type which provided the blastocysts." The Office asserts that the term "type" could be referring to breed, age, or any genotype or phenotype. The Applicants traverse the rejection. The term "type" in claim 35 is modified and defined by the following phrase "which provided the blastocysts." Thus, the metes and bounds of the claim are clear, and not indefinite.

The Office further rejects claim 52 for allegedly failing to further limit the base claim. Applicants submit that current amendments have rendered the rejection moot.

Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of rejections under 35 U.S.C. §112, second paragraph against claims 34, 35, and 52.

CONCLUSION

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,
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